# Sensitivity of the Respiratory System to Oxygen in Cats with Activated GABAergic Brain Structures

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Activation of the GABAergic system in pentobarbital-anesthetized random-bred male and female cats by intravenous injection of GABA agonist (sodium oxybutyrate or phenibut) increases the contribution of oxygen to the regulation of respiration. Hypoxia stimulates, while hyperoxia inhibits pulmonary ventilation in cats regardless of whether their breathing is of the periodic apneustic or "machinelike" type. Their respiratory response to hypoxia and hyperoxia is more pronounced than that observed before sodium oxybutyrate of phenibut injection. It is shown that respiratory reactions to these stimuli after administration of the agonists are due not to concomitant changes in the systemic hemodynamics but rather to decreased contribution of carbon dioxide to the regulation of respiration and low oxygen tension in arterial blood.

**Key Words:** *GABAergic system; hypoxia; hyperoxia; periodic respiration; chemoreception; cats*

The GABAergic system is component of the mechanism by which the central regulation of respiration is accomplished [7]. Disorders of γ-aminobutyric acid (GABA) metabolism observed under experimental or clinical conditions may give rise to certain forms of pathological respiration [2-4,6,8]. However, the precise mechanism through which the GABAergic system participates in the formation of the respiratory rhythm has not yet been identified. Transection of cranial nerves IX and X substantially lowers the GABA level in the nucleus of the solitary tract and in the dorsal nucleus of the vagus nerve [5]. This suggests that GABA is involved in the transmission of afferent information from peripheral chemoreceptors and pulmonary mechanoreceptors. In fact, we showed that systemically administered agonists of GABAergic receptors eliminate bradypnea caused by bilateral vagotomy, i.e., these agonists affect "central vagotomy" [1]. However, it remains unclear whether the GABAergic system participates in the control of chemoreceptor afferentation.

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The purpose of the present study was to examine respiratory responses to oxygen deficiency and oxygen excess, information about which enters the respiratory center from peripheral chemoreceptors via cranial nerves IX when GABAergic structures of the brain are activated.

## MATERIALS AND METHODS

The study was conducted on 18 random-bred cats of both sexes (body weight 2.2-3.9 kg) under pentobarbital anesthesia (40 mg/kg intraperitoneally). The GABAergic agonists sodium oxybutyrate and phenibut were injected intravenously at 200 and 100 mg/kg, respectively. Similar results obtained with sodium oxybutyrate and phenibut indicated that these compounds belong to the same group. A hypoxic gas mixture (10% oxygen in nitrogen) was prepared from air and nitrogen using the standard set of rotameters supplied with anesthetic apparatus. Oxygen concentration in the mixture was monitored with an ABL-330 instrument (Radiometer International). This procedure ensured an accuracy of about 1% (i.e., 10±1% $O_2$). Oxygen (100%) and carbogen (95% $O_2$ and 5% $CO_2$) were delivered directly from the

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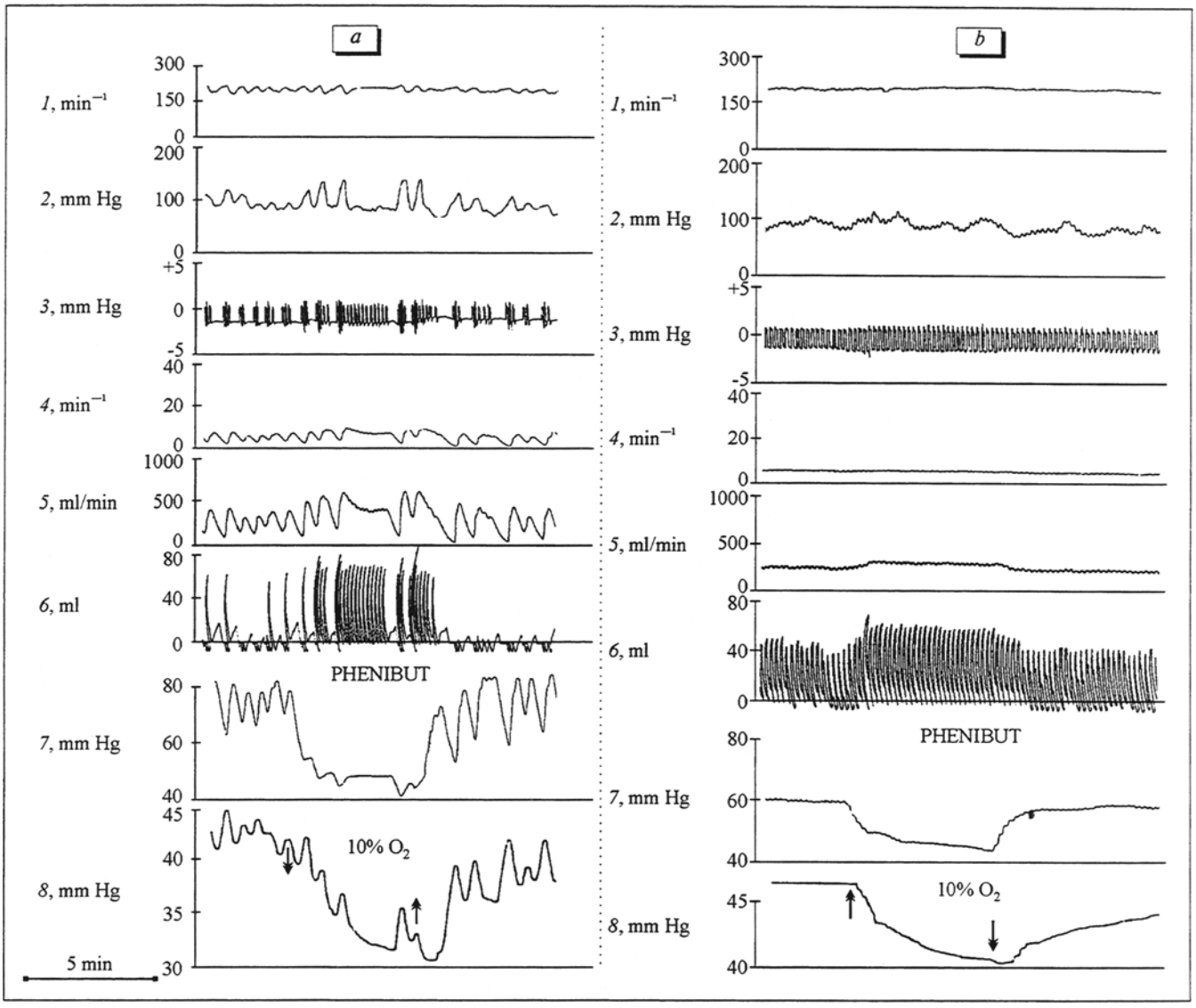


**Fig. 1.** Variations of respiration, gaseous composition of arterial blood, and systemic hemodynamics in an anesthetized cat breathing the hypoxic gas mixture during apneustic (*a*) and "machinelike" (*b*) respiration after phenibut administration. Here and in Figs. 2 and 3: *1*) heart rate; *2*) mean arterial pressure in systemic circulation; *3*) intraesophageal pressure; *4*) respiratory rate; *5*) minute volume; *6*) respiratory volume; *7*) oxygen tension in arterial blood; *8*) carbon dioxide tension in arterial blood. Arrows indicate the moment when the cat started and finished to breathe the gas mixture.

cylinders. Pure oxygen and gas mixtures were delivered for breathing only after saturating with water vapor at 38°C. The cats inhaled each gas mixture and oxygen for 5 min with intervals of at least 10 min between inhalation sessions. Experimental protocol included tests for responses of the respiratory system to hypoxia and hyperoxia before (control conditions) and after activation of the GABAergic system by injected agonist following various changes in the pattern of the respiratory rhythm (test conditions). The preparation of cats for experiment and detailed description of the procedure for measuring and recording respiratory and systemic hemodynamic parameters were described previously [1,2].

Respiratory volume was recorded on tape using the integrating chain of an MKh-01 polygraph. When the respiratory rate was low (less than 5-6 $min^{-1}$) or breath-holding was prolonged (more than 10-15 sec), the operation of the integrator became unsteady. In such cases the respiratory volume was estimated using computer monitoring, but the values were not entered into the recorder. Since the standard methods of statistical treatment envisage averaging of variables in time thereby leveling the observed periodic fluctuations of respiratory parameters and of the gaseous composition of arterial blood, these methods were not used. Some results are presented as figures reflecting typical changes in the parameters recorded

during test evaluations of the respiratory system sensitivity to various oxygen concentrations in inspired air. Each figure represents a montage of three recordings made at equal speeds of tape winding, with parameters of respiration and circulation being recorded in the system of oblique coordinates and those of blood gases in one of rectangular coordinates.

## RESULTS

Previously, we showed that changes in the respiratory rhythm following activation of the GABAergic system by a systemically administered agonist proceed in two phases [3]. Phase 1 is characterized by periodic apneustic breathing with marked breath-holdings at inspiration. After 90-120 min, periodic apneustic breathing was gradually succeeded in about one-third of the cats (depending on the individual sensitivity of the animals to the agonist) by a regular, "machinelike" breathing characterized by respiratory movements of constant frequency and amplitude (phase 2).

In both phases, we determined the respiratory system sensitivity to hypoxic hypoxia and to hyperoxia produced by inhalation of pure oxygen or a

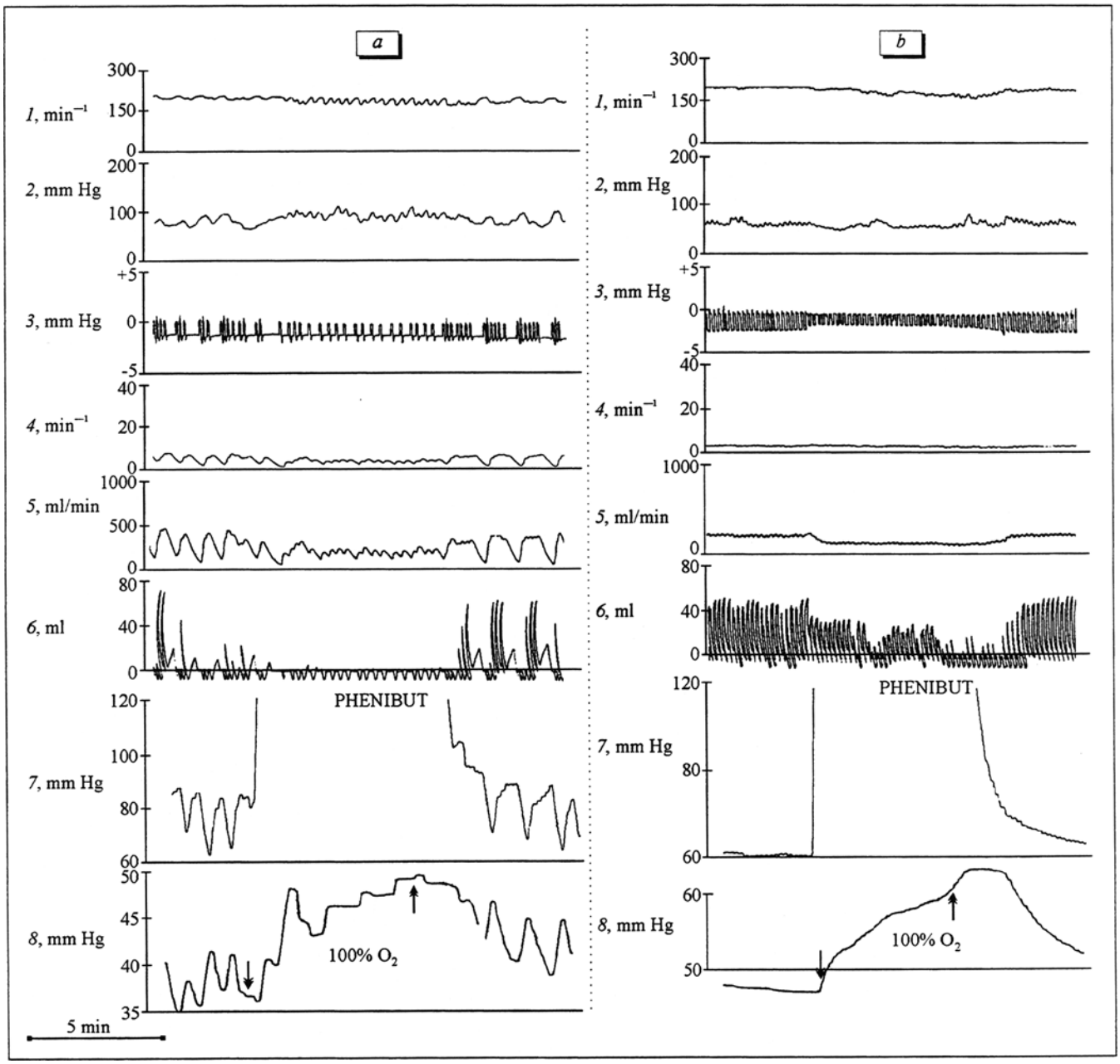


Fig. 2. Variations of respirations, gaseous composition of arterial blood, and systemic hemodynamics in an anesthetized cat breathing pure oxygen during apneustic (*a*) and "machinelike" (*b*) respiration after administration of phenibut.

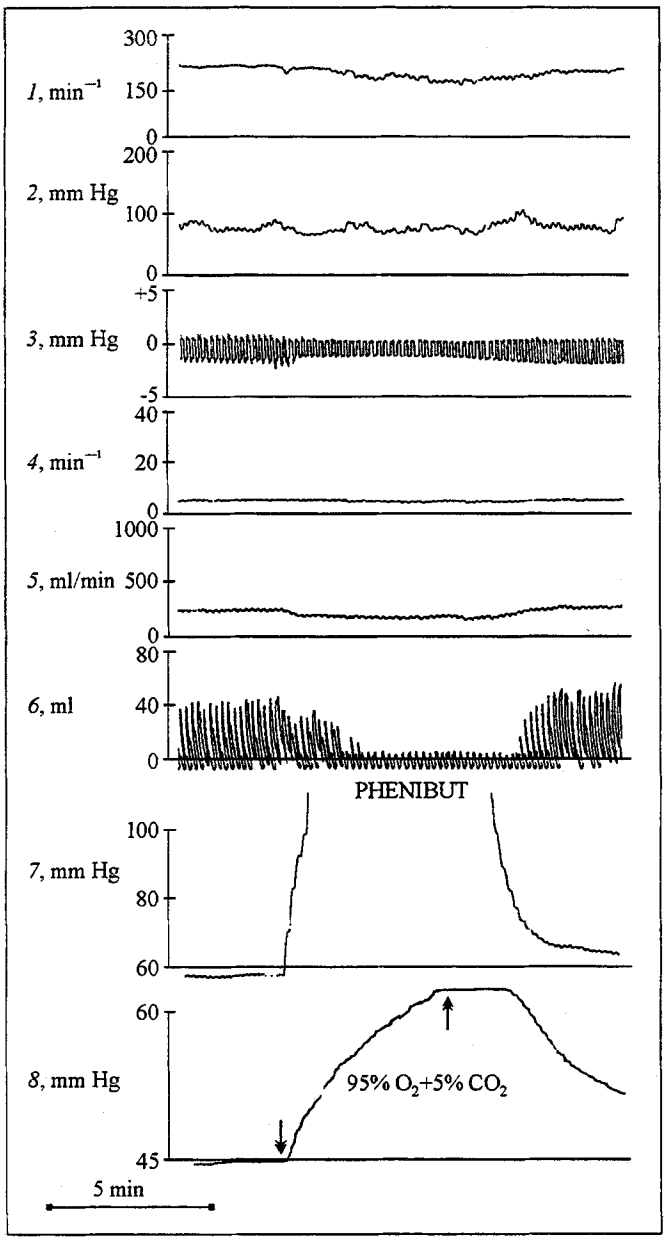


**Fig. 3.** Variations of respiration, gaseous composition of arterial blood, and systemic hemodynamics in an anesthetized cat breathing carbogen during "machinelike" respiration after phenibut administration.

mixture of oxygen and a moderate quantity of carbon dioxide (such mixtures are usually used in oxygen therapy).

During periodic apneustic respiration (phase 1), the switching from air breathing to breathing hypoxic gas mixture led to increased pulmonary ventilation, most often as a result of shortened duration or temporary disappearance of breath-holdings (Fig. 1, *a*). The respiratory rhythm prior to the inhalation of this gas mixture was characterized by a well-defined periodicity with breath-holdings lasting 30 sec or more. The intraesophageal pressure curve shows that such breath-holdings correspond to the inspiratory phase (negative pressure was maintained). This respiratory pattern is also reflected in the curves describing the minute volume and respiratory rate. Under these conditions, compensatory reactions of the circulatory system are quite evident, since both the heart rate and systemic arterial pressure are elevated during apneusis. Periodic apneustic respiration resulted in the emergence of characteristic waves on the curves of oxygen and a carbon dioxide tensions ($Po_2$ and $Pco_2$) in the arterial blood. Change to hypoxic gas mixture led to a substantial (nearly 2-fold) fall in $Po_2$ and, as a consequence of enhanced pulmonary ventilation, to a lowered $Pco_2$ in arterial blood. The heart rate and minute volume curves then became smoother. No noticeable increase in the depth of breathing was observed under these conditions. The initial respiratory pattern was restored 3-5 min after the cat stopped breathing the gas mixture.

A similar transition to hypoxic hypoxia during "machinelike" breathing (phase 2) also led to an increase in respiratory volume, while pulmonary ventilation increased exclusively due to deeper inspiration (Fig. 1, *b*).

Comparison of responses to hypoxia before and after administration of the agonists showed that stimulation of respiration was greater when this system was activated than under the control conditions. In our view, this difference was associated with the initial $Po_2$ level in arterial blood and the fall in $Po_2$ to a lower level (compared with the control conditions) during test hypoxia after injection of sodium oxybutyrate or phenibut. The arterial blood $Pco_2$ remained at a higher level, precluding hyperventilatory hypocapnia and not interfering with the development of a ventilatory response.

After the cats began breathing pure oxygen during phase 1 of the GABAergic system activation, pulmonary ventilation was inhibited to the same extent as during hypoxia, but largely as a result of decreased respiratory rate. Under hyperoxic conditions the periodic pattern of respiration was much less pronounced, but the respiratory movements were so rare that the intervals between them were comparable to the duration of breath-holdings (Fig. 2, *a*). The pronounced inhibition of respiration under these conditions also led to an increase in $Pco_2$.

Reduction in pulmonary ventilation in cats breathing pure oxygen was observed during "machinelike" breathing, i.e., in phase 2 of the GABAergic system activation. Transition to hyperoxia time was accompanied only by some decrease in the amplitude of respiratory movements whose frequency remained constant (Fig. 2, *b*).

Thus, hyperoxia in cats with the agonist-activated GABAergic system markedly inhibits respiration and appears more clearly defined than the hyperoxia in animals inhaling oxygen. This difference probably results from unequal $Po_2$ levels, which are significantly lower when the respiratory rhythm is disturbed after sodium oxybutyrate or phenibut injection.

Since carbogen, which stimulates respiration due to the presence of carbon dioxide, is used along with pure oxygen both in oxygen therapy and experimental hyperoxia, the respiratory response to this gas mixture was analyzed. In cats breathing carbogen, pulmonary ventilation is very weakly stimulated during periodic apneustic breathing (phase 1) and is inhibited during "machinelike" breathing (phase 2) (Fig. 3). Alterations in pulmonary ventilation in cats breathing pure oxygen and carbogen were similar, indicating, on the one hand, that their clinical utilities for patients with elevated activity of the GABAergic system are also similar and, on the other hand, that the respiration-stimulating properties of carbon dioxide are attenuated under these conditions.

Thus, our results indicate that changes in systemic hemodynamics accompanying changes in respiration and in blood gas composition during hypoxia or hypercapnia are not responsible for the observed respiratory pattern (Figs. 1-3). Activation of the GABAergic system potentiates the pulmonary ventilation-stimulating influence of oxygen deficiency and oxygen excess in inhaled mixture, which together with a weaker influence of carbon dioxide indicates a relative increase it the contribution of oxygen to respiratory regulation. Hyperoxia produced by inhalation of oxygen or carbogen markedly inhibits pulmonary ventilation and depending on the phase of the respiratory rhythm disturbances can reduce the frequency (down to critical levels) or amplitude of respiratory movements. Consequently, oxygen therapy in patients with abnormal respiratory rhythm due to elevated activity of the GABAergic system may weaken further their spontaneous respiration, and for this reason oxygen or carbogen inhalation sessions should be carried out with continuous monitoring of respiratory movements.

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